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THE ETIOLOGY OF SYPHILIS

BY

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OF NEW YORK

FROM
THE MEDICAL NEWS
1905

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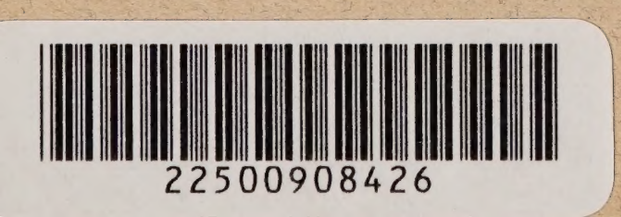

[Reprinted from THE MEDICAL NEWS, Dec. 9, 1905.]

THE ETIOLOGY OF SYPHILIS.[1]

BY SIMON FLEXNER, M.D.,
OF NEW YORK.

I AM very sensible of the great honor which you have conferred upon me in extending to me the invitation to deliver this lecture. I consider myself highly favored by it, and I regard myself also as fortunate in being able to present to you a subject of such great intrinsic interest as syphilis, and one which the experimental studies of the past several years have done so much to clear up. The history of the investigations into the cause of the infectious diseases has taught us anew that discovery in science is not an accidental occurrence; it has, indeed, emphasized the fact already established for the physical sciences, that progress proceeds along definite roads, although these roads are rarely straight and direct. There is, however, an orderly procession in discovery—the work of one era preparing the way for that of the next—although the existence of this order is not always at once apparent. The topic which is to occupy us for the next hour is a fruitful illustration of the manner in which medical discovery has come about; how by successive and careful observation a knowledge at once deep and convincing has grown up, although this knowledge has for a time rested upon data imperfectly founded.

We cannot, it is true, definitely maintain that the etiology of syphilis has been certainly and wholly resolved. And yet we are permitted to indulge the hope that this great event has possibly been achieved. We have, in any case, as a permanent addition to the knowledge of syphilis, many important facts which come to us on established grounds, and which cannot be affected by any fate overtaking the recent discovery of a spiral organism in syphilitic products.

1 The Wesley M. Carpenter Lecture, delivered before the New York Academy of Medicine, October 19, 1905.

The successful inoculation of monkeys and apes with syphilitic virus has revived interest in the question of transmission of syphilis to the lower animals. Were it merely a matter of susceptibility to infection in these animals the question would have a theoretical interest only. But when it is considered that there are many problems of syphilitic infection which have failed of solution because observation was limited wholly to man, and when it is further recalled that the experimental study of other diseases has given the keys to unlock what formerly appeared as insuperable difficulties, we are permitted to believe that the study of the difficult and tangled subject of syphilis in man may also be aided through this means.

We owe to Metschnikoff and Roux[1] the demonstration that apes are subject to inoculation with syphilitic virus. The earlier literature, as you all are aware, contains references to the possibility of communicating syphilis to different classes of vertebrates. While in most instances the attempts were regarded as failures, there are several experiments recorded for which success has been claimed. Auzias-Turenne[2] believed in 1866 that he had produced syphilis in the cat; and the next year Legros and Lanceraux[3] described specific lesions in the guinea-pig. Swine were thought especially subject to inoculation, and at one period they were used for numerous experiments. Martineau[4], Adrian[5], Hügel and Holzhauer[6] all recorded successful results; but all these mistaken observations were set aside by Neisser's[7] conclusive experiments.

The case is, however, quite different in respect to the inoculation of monkeys, which were chosen because of their closer zoological relationship to

1 Annales de l'Institut Pasteur, 1903, XVII, 809.
2 La Syphilisation, 1878, p. 422. Cited by Metschnikoff and Roux.
3 Cited by Roux and Metschnikoff.
4 Ibid.
5 Archiv f. Dermatologie u. Syphilis, 1899, XLVII, 163.
6 Ibid., 1900, LI, 225.
7 Ibid., 1902, LIX, 163.

man. Klebs[8], in 1879, was the first, I think, to employ these animals. He used a fragment of a primary lesion in man for inoculation; but this experiment is, unfortunately, unconvincing for the reason that the species of monkey is not stated, and secondary, papular lesions are described as having appeared on several parts of the body six weeks after inoculation. A second successful result is reported by Martineau and Hamonic[9], who, in 1882, inoculated a macac monkey. They say that four weeks later the animal developed primary syphilitic lesions at the place of inoculation, and these were followed by adenites and ulcerations of the mouth. There would be nothing essentially impossible in these experiments were it not that later studies have shown conclusively that the lower monkeys are not subject to the secondary stages of the disease, or, at least, that there is no similarity between the secondary phenomena as observed in man and the remote ones seen in these animals. Moreover, the studies which immediately succeed those of Klebs and Martineau were uniformly negative in result, and tended, therefore, still further to discredit the supposed successful experiments. There can, I think, be no doubt that Sperk[10] in 1886 and 1888 proved the occasional transmissability of human syphilis to the macac species of monkey. Of 46 monkeys which he inoculated, three only gave positive results. These last belonged to the macac species and were all infected with the same material. The first developed a chancre-like lesion, the beginning of which was noted twenty-four days after inoculation; from the first a second, and from the second a third animal of the same species were infected. In each instance there was a long period of inoculation, and the healing process was slow. In the second animal three months,

8 Archiv für experimentelle Pathologie, 1879, X, 161.
9 Bulletin de l'Academ. de méd., 1882, XI, 1007.
10 Œuvres complètes, t. II, Paris, 1896, pp. 614-616. Cited by Metschnikoff and Roux.

and in the third 52 days elapsed between the appearance and cicatrization of the lesions. These experiments, therefore, may be taken as proving not only the susceptibility of certain monkeys to the local lesions of syphilis, but also the possibility of successive transmission of the virus from animal to animal.

Interesting and important as these results are, they are too irregular and imperfect to serve as an experimental basis for the study of the pathology of syphilis. Since in far the greater number of tests the effects were nil, the positive results partake of the nature of accidents, with which scientific medicine cannot deal adequately. This is perhaps the reason why the subject remained so long in abeyance until interest in it was revived by Metschnikoff and Roux's[11] announcement in 1903 that the higher or anthropoid apes were subjects to syphilitic inoculation, the disease manifesting itself in the form of primary lesions, which, after an interval of time, are followed by adenitis and an eruption of syphilitic papules. In their publication they draw attention to an unpublished result of Maurice and Charles Nicolle, who also succeeded in causing in the lower monkeys local syphilitic lesions of a papular and ulcerative character.

Just as the earlier experimenters were led to employ the monkey because of its relationship with man, so were Roux and Metschnikoff led to their choice by considerations of closer zoological approximation. The choice of the chimpanzee was peculiarly fortunate. This species has proven to be readily subject to inoculation with the virus of syphilis, to which it reacts in a constant and characteristic manner. Hence the chimpanzee is adapted for those refined experiments which have already extended, and, doubtless, will still further extend our knowledge of the nature and mode of action of the syphilitic poison.

11 Annales de l'Institut Pasteur, 1903, XVII, 1809.

Since this subject is of such great theoretical and practical interest, it may be permissible to describe briefly one or two successful experiments. The first ape inoculated was a female chimpanzee about two years old. The source of the virus was (1) serous fluid from a chancre in man, and the site of inoculation the prepuce of the clitoris; and (2) material from a mucous placque, and the site of inoculation the border of the eye-brow. Five days after the first inoculation a second one was made with virus from a chancre. The original scarifications quickly healed, after which no visible lesions appeared until the twenty-sixth day following the first inoculations. A small vesicle, which later increased in size and took on indurative characters, was noted on the prepuce at this time. The fully developed lesion was examined by Fournier, du Castel, Hollopeau and Marc Sèe, who pronounced it a hard chancre. It had been noted at the time of inoculation that the lymphatic glands of the groin and elsewhere were not readily palpable; with the appearance of the local lesion the lymphatic glands of the groin could be easily felt, and some days later they had increased in volume, those on the side of the ulcer being the larger.

Just one month later, that is fifty-six days after the first inoculation, papules were noted upon the thighs, abdomen and back. They numbered fifteen, were round and of the diameter of a five-cent piece. The peripheral zone was at first red, and later became pigmented; the mid zone was paler; the center came to be covered with a scaly crust. On scratching, serum was exuded. The papules endured for a month and then began to heal; but they were still visible some weeks later, at the time of the death of the animal, which was caused by the pneumococcus, to which microorganism the chimpanzee in confinement is peculiarly susceptible.

This result points a new direction in which to pursue the experimental study of human infec-

tious disease. In many instances there is only a rough analogy between the natural disease in man and the counterfeit produced in the lower animals. That our knowledge of infectious diseases, perhaps even of other diseases not now open to experimental study, might possibly be greatly extended by the use of animals which are more closely related to man than the usual laboratory ones, can hardly be questioned. The difficulties in the way of accomplishing such an undertaking on a large scale are immense and not readily to be overcome. We detect, however, a still further justification for their use in the successful experiment of Greenbaum,[12] who would seem to have removed the last traces of doubt which surround the typhoid bacillus, by successfully causing in a chimpanzee typhoid fever by feeding cultures of the bacillus. And Charles Nicolle[13] has just announced from the Pasteur Institute at Tunis the production of lepromata in two specimens of *Macacus sinuensis* by inoculating leprosy tissue into the skin.

Metschnikoff and Roux immediately showed that the syphilitic poison was transmissible from ape to ape without undergoing alteration of quality as measured by the effects produced. Forty-five days after the appearance of the primary lesion in the first animal a second was inoculated from the first—both from the primary and the secondary papular syphilides. Lesions regarded by Fournier as syphilitic developed from both inoculations, and they were followed by adenitis. In a later report they describe still another important experiment in the chimpanzee. Eighteen days after the appearance of a primary lesion, which was located on the eye-brow, small persistent erosions appeared on the tongue, and three weeks later still other lesions appeared there and on the lower lip. These erosions were regarded as mucous placques. At about the same

12 Cited by Metschnikoff.

13 Comp. rend. des Séances de l'Acad. des Sciences, 1905, CXL, 539.

time this animal developed a paraplegia lasting more than a month, which, it is suggested, was of syphilitc origin.

Lassar's[14] experiments, while confirming the foregoing, extend them very little. He observed the regular development of the primary lesions, the delay in appearance of the secondary manifestations, and the transmissibility of the virus from animal to animal. He describes secondary, luetic papules on the hands and feet and about the anus, and he describes in a brief way a histological study of the experimental syphilides by Becker and Mayer,[14a] which bring them into agreement with the corresponding lesions in man, a conclusion to which they arrived and one which was confirmed by Arnal and Salmon,[14b] who studied Metschnikoff's specimens. Certain experiments which I performed upon monkeys, to which I will refer later, enabled me to make out the essential identity of the experimental and the naturally acquired primary lesions.

The studies made by Neisser[15] confirm and extend those just mentioned. Neisser would seem to have discovered an interesting gradation of susceptibility to syphilitic infection in the ape, depending upon the exact position held by different species in the zoological series. His conclusions are that the lower monkeys react with local syphilides, the highest monkeys, namely, the chimpanzee, gorilla and orang-utan, all react with primary and secondary lesions, while the gibbon, which occupies an intermediate position, develops less characteristic primary lesions and fails to show the typical secondary ones.

There is at least one important way in which the results of Neisser's experiments differ from those of Metschnikoff and Roux. The latter experimenters believe that they had modified and

14 Berliner klin. Wochenschrift, 1903, XL, 1189.
14a Included in Lassar's paper.
14b Annales de l'Institut Pasteur, 1904, XXIII, 465.
15 Deutsche med. Wochenschrift, 1904, XXX, 1369, 1431, and with Baermann, idem., 1905, XXXI, 748.

attenuated the virus by its passage through the lower monkeys so as to produce a vaccine which, when used to infect the chimpanzee, provoked a local process, and left this animal protected from the virulent human virus. Neisser, on the contrary, has inoculated successfully not only from monkey to monkey, producing the local lesions, but from monkey to anthropoid, with the production both of the local primary and the systemic secondary infection. Hence he concluded that Metschnikoff's failure was due not to protection, but to syphilization of the chimpanzee.

Doubtless the higher apes will come in time to resolve many disputed points in human syphilis, and to supply facts where we now have opinion and conjecture. The use of these animals has already answered partially certain questions relating to the manner of entrance of the virus into the body and the comparative virulence of different products of the syphilized animal; and it may also help to explain better than we now know it the important questions of re-infection in syphilis. Cutaneous inoculations with primary syphilides and primary lymphatic glands cause lesions; subcutaneous injections of chancres and condylomata produce no specific manifestations; insertion of infected lymph glands directly in the peritoneal cavity is without effect. Defibrinated blood and blood serum from cases of recent syphilis in man are innocuous when injected subcutaneously and intraperitoneally. Blood serum from syphilitics is also without protective action against subsequent inoculation with active virus. The internal organs—spleen, liver, bone-marrow—of the recently infected monkey and ape possess neither infective nor protective properties of high degree. Perhaps they are wholly innocuous. These are some of Neisser's results, which, if not conclusive, have yet a bearing upon the relative infectiousness of the blood and internal organs of syphilitics, and bear on the questions of the avenue through which the virus

seeks to enter the body, and its capacity to enter directly into the interior of the body and cause the secondary lesions of the disease, without first having undergone incubation or other changes at some local superficial site.

That the virus of syphilis when separated from the body is labile is shown by the relative infrequency of accidental infections from contaminated objects. We have no data with regard to the influence upon the virus of simple drying and exposure to the air; but these are now easily within reach. It has been ascertained by Metschnikoff and Roux[16] that the poison is easily injured or destroyed by low degrees of heat. Particles of chancres and condylomata suspended in salt solution, or in aqueous tumor, are rendered inactive upon the monkey and chimpanzee after heating for one hour at 51° C. and half-hour at 60° C. Glycerine,[17] on the other hand, does not deprive the virus of its power to set up specific lesions in apes, at least not when the inoculation is made soon after mixing.

The foregoing studies have been valuable in establishing many points regarding the pathology of syphilis, but they have thrown no light upon the nature of the micro-organism which it is hardly presumption to speak of as its immediate cause. That this micro-organism is not so peculiarly specialized as to thrive on human tissue alone is now proven, and the fact of the blood relationship of the whole group of primates receives through these studies an additional and unexpected confirmation.

No one doubts that the cause of syphilis is a living germ, but its elusiveness up to the present time has given rise to speculations upon its probable size. Now that we have learned that a class of micro-organisms exists which defy the highest powers of the microscope and that among this class are several species causing fatal infections

16 Annales de l'Institut Pasteur, 1904, XVIII, 657.
17 Metschnikoff and Roux, idem.

in the lower animals it is pertinent to inquire whether the micro-organisms of syphilis also belong here. This question has been answered indirectly by filtration experiments carried out by Metschnikoff and Roux.[18] They proved that an unglazed filter, which will permit the passage of the microbe of pleuro-pneumonia of cattle, holds back the virus of syphilis; and even before this conclusive test was made Klingmüller and Baermann[19] had inoculated themselves unsuccessfully with filtrates obtained by the use of Berkefeld filters from active syphilitic lesions. In other words, the evidence all points to the microbe of syphilis being microscopic, not ultramicroscopic.

There has been, as you well know, no dearth of supposed discovery of the microbic cause of syphilis. It would not be profitable to make an historical and critical survey of the general literature of the subject, for all the earlier observations down to the publication of Siegel and Schaudinn and Hoffmann have either been discredited or stand upon a foundation so weak as scarcely to call for painstaking attempts at confirmation. The very far-reaching results of Siegel's[20] studies, embracing, as they do, besides syphilis, smallpox, scarlet fever and foot and mouth disease, have not yet received the attention which they possibly deserve by reason of the faith which F. E. Schultze[21] has expressed in them. It is, however, interesting to learn that the discovery of *Spirochæta pallida* is the direct outcome of an attempt on the part of Schaudinn and Hoffmann to confirm Siegel's observations on the

18 Ibid. See also Siebert (Deutsche med. Wochenschrift, 1905, p. 1642).

19 Deutsche med. Wochenschrift, 1904, XXX, 766.

20 Untersuch. über die Aetiologie des Syphilis, Anhang zu den Abhandlungen der königl. preuss. Akademie der Wissenschaften vom Jahre 1905; Untersuch. über die Aetiologie der Pocken und der Maul- und Klauenseuche, idem.; Untersuchungen über die Aetiologie des Scharlachs, idem. Also in Münch. med. Wochenschrift, 1905, LII, 1323, 1384, 1574; Medizin. Klinik, 1905, I, 446. See also Freund, Münch. med. Wochenschrift, 1905, LII, 1819.

21 Berlin. klin. Wochenschrift, 1905, XLII, 653.

so-called protozoon, *Cytorrhyctes luis,* which he described as existing in the blood and tissues of syphilitic patients, and in rabbits inoculated with the blood and other products obtained from them.

In view of the late developments on this subject it will not be uninteresting to quote from the last paper of Metschnikoff and Roux[22] and to give their views upon the nature of the syphilis microbe. Their words shows that they looked for the very form of organism that was afterwards found. They say: "The microscopical researches which we have made have not yielded us satisfactory results. A minute examination of the serous fluid obtained from initial vesicles revealed the presence of leucocytes and red blood corpuscles, but no microbes. The minute granules in the fluid—cell fragments, doubtless—do not execute any movements attributable to shock from a motile organism. If the parasite of syphilis were a *spirillum* much smaller than that of Obermeier or the spirillum of birds, one should have been able to detect its presence by the movements imparted to the corpuscles suspended in the serous fluid. The absence of this movement makes us suppose rather that the organism is immobile. Moreover, the addition of neutral red to the serum, which, in the case of the spirillum of birds, makes it at once apparent, accomplishes nothing in the study of the microbe of syphilis."

It is more than noteworthy that within six months of the appearance of this utterance a spiral organism should have been discovered in syphilis, and before the lapse of another half-year been established as not impossibly the cause of the disease. There is, however, more or less of justification to be found for the view expressed by Metschnikoff and Roux for the spirochæta of Schaudinn and Hoffmann[23] is not actively mo-

22 Annales de l'Institut Pasteur, 1904, XVIII, 661.

23 Vorläufige Berichte über das Vorkommen von Spirochæten in syphilitischen Krankheitsproducten und Papillomen. Arbeiten a. d. kais. Gesundheitsamte, 1905, XXII, 526; Deutsche med. Wochenschrift, 1905, XXXI, 711; Berliner klin. Wochenschrift, 1905, XLII, 673. Also, Hoffmann, Berliner klin. Wochenschrift, 1905, XLII, 726 and 1022; Schaudinn, idem., p. 733.

bile, and its extreme tenuity and refractoriness to staining agents renders it difficult to see, both in the stained and unstained conditions.

In order that one may fix accurately the historical position of the spiral organism of Schaudinn and at the same time be informed of the degree of prescience contained in Metschnikoff and Roux's conjecture, it may be stated that as early as 1903 Bordet and Gengou[24] observed very fine spiral organisms in the interior of a chancre and in a mucous patch. Doubtless these spirals were identical with the so-called *Spirochæta pallida;* but as subsequent examinations did not yield these investigators the same parasite they ceased to regard it as important. That this observation was familiar to the staff of the Pasteur Institute is certain, and the recent history of the spiral organism occurring in syphilis also suffices to explain Bordet's failure to demonstrate it constantly in the lesions.

The flood of confirmatory publications upon the discovery of Schaudinn and Hoffmann has created a feeling of faith in the spirochæte which its discoverers have never publicly expressed.[24a] It will be our task at this time to pass in review the evidence upon which this faith is based in order that we, too, may appreciate the force and the direction of the currents.

Spirochæta pallida is described by its discoverers as measuring from 4 to 10 microns, the average length being 7 microns, or about that of a red corpuscle of man. In width it varies from unmeasurable thinness to ½ micron. It posseses from 3 to 12, sometimes more, curves, which are sharp and regular and resemble the curves of a corkscrew. The poles are sharpened. The or-

24 Metschnikoff and Roux, Bull. de l'Académie de Méd., 1905, LIII, 468; and Bordet, Soc. roy. des Sciences Méd. et Nat. de Bruxelles, 1905, LXIII, 124.

24a In papers which appeared after the reading of this address Hoffmann (Deutsche med. Wochenschrift, 1905, p. 1455) and Schaudinn (idem., p. 1665) state it as their conviction that the pallida is the definitive cause of syphilis. Metschnikoff (Bull. de l'Institut Pasteur, 1905, III, 544) expresses confidence in the discovery, and views syphilis as a chronic spirillar infection.

ganism is mobile and the motions consist of rotations on the long axis, forward and backward movements, and bending of the entire body. Flagella have not been seen.[24b]

The character of the curves and the tenuous forms give a striking appearance to the organism, and make its identification relatively easy. As it is frequently the only spiral organism present in the preparation, there is, as a rule, no difficulty surrounding its identification. But its detection is not entirely easy, since with most stains recommended for its demonstration it is tinged so lightly that some practice is required in order to see it. Its admixture on the ulcerating surfaces of syphilides with other spiral organisms, not limited to specific lesions, but occurring in ulcers of various kinds, adds somewhat to the difficulties of its detection. The most trustworthy evidence points to the fact that in the interior of specific lesions this pale spiral organism is rarely attended by the coarser kinds of spirilla or with extraneous bacteria; and, therefore, the fluids obtained from the interior of the syphilides are the most favorable for purposes of examination. Several writers have stated that the pallida may be entirely missed among the saprophytes of the surface of ulcerating lesions under conditions in which it is easily detected in the deeper parts. My own study of ulcerating primary lesions, condylomata and mucous patches, has led me to similar conclusions. There is, I think, no doubt that the pallida occurs on the surface of these lesions, but evidently its growth is more restricted than in the absence of contending saprophytic, pyogenic and putrefactive micro-organisms. The pallida would seem, therefore, not to thrive as

24b This statement requires modification since Schaudinn (Deutsche med. Wochenschrift, 1905, p. 1665) demonstrated by means of Loeffler's stain flagella upon the pallida. The coarser and certain finer indeterminate spirochætæ, when stained in this manner, gave evidences of undulating membrane, but not of flagella. Herxheimer and Löser (Münch. med. Wochenschrift, 1905, p. 2212) also give figures of the flagellated pallida which they obtained by the use of the ordinary dyes, apparently anticipating Schaudinn's finding.

well on dead as on living tissue, a consideration which is not insignificant in view of the growing belief in its peculiar pathogenic and highly parasitic properties.

Foreign and distinct spiral organisms occur not infrequently in health about the genitals, and probably in other parts of the surface of the body, and these kinds may therefore become associated in specific lesions with the pallida. The chief foreign spiral organism of this class is a coarser spirillum with fewer curves of wider and less sharp contour. It has been described several times, especially in inflammatory venereal processes, by Berdal and Bataille, Csillag and Rona;[25] and Schaudinn and Hoffmann have proposed tentatively for it the name of *Spirochæta refringens.* It appears to be a common and widespread saprophyte.

A few of the more recent writers have described among the paler and more delicate spirals certain forms in which the curves are longer and a part of the rod is straight. These they consider as possible transitions between pallida and refringens. Although my study has not been exhaustive, I may mention that I have not observed such transitions in the syphilitic material which I have studied, and the impression I have gained is that these two types are quite distinct.

There is, however, evidence at hand, to which I will refer more in detail later, that the pallida type may be simulated more or less closely by spiral micro-organisms occurring in other pathological conditions than syphilis. Everyone knows the dangers and difficulties which attend every attempt at classification of these minute organisms upon morphological and staining characters chiefly. But until a method of cultivation is found, and we are without one at present, we must rely as best we can upon superficial character. I am convinced that the morphological

25 Quoted by Schaudinn and Hoffmann. Arbeiten aus dem kaiserlichen Gesundheitsamte.

characters of the pallida are sufficient to identify it in specimens made from specific lesions; but I should not be surprised were it found that similar morphological forms occur in nature among the saprophytic micro-organisms.

Since it will be an impossible undertaking to review even most briefly the separate papers which have appeared on the *Spirochæta pallida,* I will endeavor to give you the spirit of the studies already published, as I understand it. The lesions which have been studied chiefly are those which appear on the surface of the skin and mucous membranes, but, nevertheless, a small number of observations have been made on the blood and deep organs, while a fairly large number have been carried out with material obtained from the superficial lymphatic glands.

The evidence is conclusive that primary lesions —condylomata, papular, macular and pustular superficial lesions—contain the pallida either constantly or in the majority of cases. The later papers record fewer failures in finding the organism in chancre, condylomata and mucous patches than the earlier ones; and I think there can be no doubt that this greater constancy is to be attributed to increased experience in the observers, and to improved methods of staining the organism. There is something elusive and mysterious in the varying capacity for taking up stains exhibited by the pallida. My first successful preparation was obtained with an ordinary gentian-violet dye; but I failed with this same stain in many subsequent trials. Azur still remains, I think, the most reliable stain, although several of the more rapid methods, in particular that of Proca and Vasilescu, are also useful.

Since the choice of material will affect essentialy the result of examination, I may be permitted to say a word upon this subject. If it is desired to study ulcerative lesions the surface should first be cleansed, after which the raw surface exposed need only be gently rubbed with

a platinum loop in order to obtain a few drops of serum. The cover glasses should be spread as thinly as possible, which is the rule for all these examinations. Should ulcerations of the superficial syphilide not have taken place a few drops of fluid—a mixture of blood and lymph—can be withdrawn with a hypodermic syringe. In the case of mucous patches I have preferred to use the double sharp spoon, removing with one the superficial necrotic tissue and saprophytic organisms, and with the other scraping lightly the denuded surface. This operation is quite painless, but there is no disadvantage in previous cocainization of the surface if it is desired. I have compared the two scrapings, always to the advantage of the deeper one, in which, greatly to my surprise, I often found, except for the pale spiral, almost complete absence of micro-organisms. These ulcerated papules of the mucous membrane of the mouth and throat would seem, from my experience and from reported examinations, to contain the spirochæta in good numbers, and hence to be particularly suitable for demonstrating the organism. I have found no difficulty in distinguishing in these preparations from the buccal cavity the pallida, and I have not been disturbed or put in doubt by any appearance of transition to the common spiral organisms of the mouth. For much of the material studied I must thank the kindness and courtesy of the staff of the City Hospital.

Through the kindness of Dr. Pedersen, of the House of Relief, I was able to secure early in my studies several excised chancres and condylomata. These served not only to supply me with favorable specimens for demonstrating the pallida, but they enabled me to compare the findings from the superficial and deeper layers of the same specimens, which I did to the advantage of the latter.

The skin lesions—papules, pustules and roseolous areas—are often rich in the organism. After

cleaning the surface a superficial incision with a scalpel or sharp needle is made, and a drop or two of blood and lymph expressed.

The superficiality of the three classes of lesion described make them easily accessible for diagnostic purposes. I assume that should the *Spirochæta pallida* be established as the cause of syphilis, for which I may add I think the evidence still inadequate, its presence will be sought systematically to confirm or prove the diagnosis. I am unable, from my lack of clinical experience, to discuss the question of the probable advantage to the patient in doubtful cases which might accrue from an earlier diagnosis and more prompt treatment. It seems to me not improbable that valuable time may not only be saved in this way, but possibly some of the distressing and disfiguring stigmata of the disease might be avoided.

I was able recently to try the value of this theoretical diagnostic test. The case was that of a respectable woman (Abbott) forty years old, who presented herself because of an eruption on the face which spread to the shoulders and slightly to the abdomen and back. She denied stoutly exposure to infection with syphilis; and as the eruption, although a rosy-macula, was not unmistakeably characteristic, she was being observed prior to the institution of treatment. The examination of blood taken from a slightly raised spot on the back gave a fair number of the pale spiral organisms. Of course, no practical significance can at present be attached to this observation.

The spirochætæ have been demonstrated less uniformly in the deeper organs. The locally enlarged lymphatic glands, those of the groin chiefly, which show early involvement in syphilis, were naturaly studied immediately. The result of this study has been to furnish a positive answer as regards their presence; but while Hoffmann has succeeded practically constantly in staining

the organism in aspirated gland juice, others have been less successful. My own experience taught me that the spirochæte occurs in gland juice; but that long search may be required to discover it. I have always endeavored before staining to obtain aspirated fluid which contained masses of gland cells, since the blood alone is not likely to yield the organisms. By using a needle of good caliber and moving it slightly to and fro in the massaged gland, an operation which, once the skin is punctured, appears to be nearly painless, and using a syringe of 5 to 10 cubic centimeters' capacity, so as to secure strong suction, a few drops of blood-stained gland juice can be obtained. This may, as Hoffmann[26] suggests, be ejected into a porcelain dish or capsule, preferably at two or three points, and the small whitish, rather than the reddish drops, chosen for examination, since they will contain the gland tissue in greatest amounts. I think any dilution of this fluid objectionable. Thin spreads on cover glasses of the pure fluid should be made. I was obliged in some instances to dilute this fluid with salt solution in order that it might be used for some attempts at cultivation of the organism. These cover-glasses were not satisfactory.

It is too early to pass upon the value of negative examinations, but one experience which I had at first troubled me and then taught me a great deal.[27] It showed me the value—in this instance the invaluableness—of tenacity. A young man of eighteen (Case IV) acquired a venereal infection in January. I saw him in May at the House of Relief. The primary lesion, excised by Dr. Pedersen, showed the pallida. I aspirated an enlarged inguinal gland and studied the specimen in the fresh state and discovered what I took to be several small and one large faintly motile spiral organism. I could not be certain of my observation as the organisms were

26 Berliner klin. Wochenschrift, 1905, XLII, 1022.

27 Flexner and Noguchi, THE MEDICAL NEWS, 1905, LXXXVI, 1145.

very difficult to resolve satisfactorily. I was therefore not greatly surprised to find no spirals in the stained preparations, and I was led to suspect that I had been deceived by the first examination. Later, however, after a more searching study of the stained specimens, I discovered a small number of the pallida.

The finding of the pallida in the regional lymphatic glands is, of course, imperative if the organism is to have any position as the probable cause of syphilis. My experience, which has not been large, has not suggested that the enlarged inguinal lymphatic glands contain an indiscriminate mixture of organisms. I have not found such mixtures in cover-glasses, and they have not developed in cultures made from gland juice. The question now arises as to whether this organism also invades the deeper parts of the body. Can it be found in the spleen, etc., and does it inhabit the circulating blood? Our knowledge upon this topic is still highly defective. Schaudinn found the organism once in aspirated splenic juice from a case of recently acquired syphilis; Hoffmann has obtained it from the aspirated juice of an enlarged submental gland in a case in which a chancre of the lip existed, which is, of course, equivalent to the findings in the glands of the groin. The circulating blood has been studied by several investigators, but with a very small number of successful findings. Reckzet[28] was the first to report the pallida in the blood, but the forms which he saw were not typical, and he regarded them as degenerating spirals. Raubitschek[29] reports a positive finding in a woman who dated the infection three months before the examination. Perhaps the most convincing results were obtained by Noeggerath and Staehlin[30] with centrifugalized blood diluted 1

28 Cited by Hoffmann, Berliner klin. Wochenschrift, 1905, XLII, 1022.
29 Wiener klin. Wochenschrift, 1905, XVIII, 752.
30 Münch. med. Wochenschrift, 1905, LII, 1481.

to 10 with 0.3 per cent acetic acid. They employed 1 cubic centimeter of blood for the test, and report three successful observations. Sobernheim and Tomasczewski[31] examined several specimens by this method, and failed in all but one.

I have studied the blood from two cases: the Abbott woman and a man in whom a macular rash had only just appeared, the primary infection having exhibited itself six weeks before. The blood in the first instance was taken from the lobe of the ear, and in the second from the median basilic vein. In neither were organisms found in the centrifugalized specimen. It is, perhaps, not necessary to state that precaution must be exercised in selecting a part of the skin which is free from the localized lesions of the disease from which to obtain the general blood. I may be permitted to refer in this place to a recent demonstration of the spirochætæ in the skin lesions of varicelliform syphilis by Hoffman.[32]

A review of the facts which have now been brought to your attention leads to the statement that a particular and apparently peculiar spiral micro-organism has been found with striking constancy in the primary and secondary focal lesions of acquired syphilis, whether the lesions are situated on the surface or imbedded beneath the skin of the body. This review also tends to show that this organism does not exist in large numbers in, and possibly is only an occasional and accidental inhabitant of, the general blood stream in the disease, which fact is in striking conformity with Neisser's experiments on the non-infectivity of the blood of syphilitics for monkeys.[32a] There is, however, abundant evidence of the distribution of this micro-organism by the general cir-

31 Idem., p. 1857. See also Hoffmann, Deutsche med. Woch., 1905, p. 1710.

32 Berliner klin. Wochenschrift, 1905, XLII, 1022.

32a In a recent communication Hoffmann (Berliner klin. Wochenschrift, 1905, p. 1450) reports a successful inoculation of syphilis in a macacus rhesus, with the circulating blood from a man who acquired the disease six months previously and was untreated. The experimental lesion showed many pallida.

culation, from which it would appear to be taken out by the blood-vessels of the skin and mucous membranes, and possibly the internal organs.

Whether the spirochætæ remain in the vessels of the skin or whether they quickly pass into the surrounding lymphatics is not known. It seems, however, for the moment permissible to assume that the inflammatory and productive lesions are associated with, perhaps caused by, this localization; although it must for the time being remain unsettled whether the direct causes of the local reaction are vascular emboli or perivascular infections.

This doubt will in all probability remain until by histological methods we are able to stain the organism in the tissues. But I have endeavored to procure a tentative answer to this question in another manner, namely, by producing rapid vesication with ammonia water and studying the serous fluid. Since the vesicles arise in a few minutes and the fluid is free of blood corpuscles, I thought it possible that any spirochætæ which were lying about the vessels in the tissue spaces might be washed into the vesicle. A study of vesicles produced in three subjects of the skin lesions of early syphilis were, however, all negative. On the other hand, it appears from tests made later by Levaditi and Petresco[33] that a more severe vesication is accompanied by the escape of spirochætæ in the vesicular fluid. The vesicant was kept applied by him for eight hours, after which time many organisms were found to have passed out. He found the largest number in vesicles directly over papular syphilides, a smaller number in the skin immediately surrounding the lesions, and none in the distant healthy skin. Since in vesicles many hours old cellular exudation has taken place it may be assumed that the injury to the blood-vessels is greater than occurs with the rapidly acting ammonia; and hence it is possible that the previous vessels permit the es-

33 La Presse Médicale, 1905, No. 78, p. 617.

cape with the serum and cells of some of the micro-organisms which they may contain. This method of Levaditi has, however, the advantage of furnishing a fluid rich relatively in spirochætæ for diagnostic purposes.

Before the employment of bovine virus was as general as it now is syphilis was occasionally transmitted by vaccination. While this danger has been eliminated by the substitution of bovine for human virus, it would be of interest to determine whether the pallida exists in vaccine pustules in syphilitic subjects, since its detection there would not be without theoretical significance. I have looked for the pallida in vaccination lesions in two syphilitic persons thus far without success. The cases were perhaps not especially favorable, for in one the crust was dry and almost ready to come away, and in the other the vesicle was partly dried and contained thick purulent exudate unfavorable for study. I mean to persue this investigation farther as soon as a favorable opportunity offers.

The great length of time during which the micro-organism of syphilis must, under some conditions, endure in a living state in the body, constitutes a fact of high importance in the history of the recurrences and the congenital transmission of the disease. Hence the question arises whether there is reason to believe that congenital syphilitic manifestations are associated with the occurrence of the pallida, whether the number and distribution of this organism are such as to explain the lesions and the infectiousness of this disease, and whether the spirochæte exists equally in those cases of congenital syphilis which are the offspring of a parent suffering with florid syphilis, and of another in whom the disease has not manifested itself for many years. We are, fortunately, in a position to state that the evidence at hand indicates that the spirochæte survives in the body for many years and is transmissible by a parent herself free from the usual signs of the

disease. I can best support this statement by citing one or two illustrative examples:

The first will show that the pallida appears in the late secondary lesions, although several years have elapsed since infection. Sobernheim and Tomasczewski[34] report three cases of syphilis in which infection occurred in 1898, 1900 and 1901, respectively. In the three recurrent secondary lesions reappeared recently, chiefly on the face—nose, lip and eye. In one of the cases an ulcerating condyloma alone was present. The pallida was found in the ulcers in all the cases. The number of the organisms was not large; and it would therefore seem that in these cases the multiplication is, perhaps, restricted, as we either know or suppose to be true of certain bacterial infections, for example, the persistent infection of cartilage and gall-bladder following typhoid fever. If this view is true, then the immature tissues of fetuses and young infants must be far more favorable to free and unrestricted developments of the pallida. The literature already contains the records of a sufficient number of examinations of infants, the subjects of congenital syphilis, to show that the pallida regularly occurs in the disease. This micro-organism has been detected in the lesions of the skin and internal organs, sometimes in large, sometimes in small numbers. In several cases studied after death a general infection with the pallida could be demonstrated.

My own experience is based upon the study of two congenitally syphilitic children, for which opportunities I have to thank Dr. Cragin and his resident, Dr. Ryder, of the Sloane Hospital. The first was a living child, presenting a roseolous and papular rash. A few drops of blood were expressed from an incised macule of the foot; it was very rich in spirochætæ. The history of this child bears upon the questions suggested above—the persistence of the organism in a viable state

34 Loc. cit.

in the body through a number of years, and its freer growth in infantile tissues. The mother was thirty years old and had borne three children. The first, born nine years before, is healthy and now living. She believes that eight years ago she contracted syphilis from her first husband; she had a roseolous rash and was treated for a short time. Five years ago she miscarried. She remarried a year ago, and at present she is free from visible signs of syphilis. The father is believed to be free of the disease. This case presents nothing very unusual in the lapse of several years between the time of infection of the patient and transmission to the offspring; but in view of the subject-matter before us it assumes an especial importance as bearing on the etiological position of *Spirochæta pallida.* The placenta of this child was also examined, and after long search a single pale, spiral organism was found.

The second child of my study was born prematurely to a mother showing unmistakable signs of syphilis; it lived three-quarters of an hour. There were marked syphilitic visceral and skin lesions. The pallida was found quite numerously in the skin, but it was found in very small numbers and only after long search in the liver. The bile, it may be mentioned, showed the organism in small numbers.

That congenitally syphilitic children are capable by suckling of infecting with syphilis healthy persons is, of course, established, and it is in conformity with this fact that Babes and Panea[35] could demonstrate the pallida in the pharyngeal secretions of a congenitally syphilitic child. They also found them, I may remark, in the conjunctival secretion.

So far, therefore, as a study of congenital syphilitic lesions can serve to confirm and establish spirochætæ pallida as the cause of syphilis, this has been done in part. Doubtless many more examinations will be made, through which im-

35 Berliner klin. Wochenschrift, 1905, XLII, 865.

portant data—whether pointing one way or the other—will be accumulated. Perhaps these data will serve to bear upon the question, still perhaps not wholy settled, whether the placental circulation is or is not previous to syphilitic virus, and thus to shed an illuminating light upon those cases in which the child has presumably become infected from a post-conceptional infection in the mother; and, now that we are indulging our hopes, some light may be thrown upon that remarkable condition of supposed immunity, or of cryptic infection, which is embraced in Colles' law.

It may perhaps be objected that in this presentation I have appeared to assume that *Spirochætæ pallida* is the cause of syphilis, and that I have made this idea agree with certain facts of syphilitic phenomena. I should deplore having produced this impression; for while I have as a part of my theme considered the relation of the pallida to syphilis, I am still far from having myself a conviction of its position as immediate cause of that disease, for the establishment of which casual relation more stringent proof than yet produced will be required.

No consideration of the etiology of syphilis would be complete without reference to the late or tertiary lesions of the disease. So far as our present purpose is concerned the subject of these supposedly non-infective lesions can be dismissed with a sentence: A small number of gummata and other tertiary syphilides have been studied for the pallida with almost constant negative results. The exceptions to this rule must, I think, for the present be viewed with suspicion. No account can, of course, be taken in this connection of the study of gummata occurring in congenital syphilis, because of their close association with secondary lesions.[35a]

35a Schaudinn (Deutsche med. Wochenschrift, 1905, p. 1665) thinks it probable that the pallida may occur in the late lesions in a resting form of different appearance than the usual spiral form. Finger and Landsteiner (Sitzungsberichte der k. k. Akad. der Wissenschaft in Wien, CXIV, Abt. III, June, 1905) reported a successful transmission of syphilis to the monkey by means of inoculation of a large amount of gummatous material.

However these findings in tertiary lesions may impress you they can hardly bear very finally upon the question of etiology. There is, however, another set of observations which may have greater significance. I refer to the finding of the pallida in experimental primary syphilides in monkeys. I have had three successful inoculations of syphilitic virus upon two macac species of monkey—the rhesus and cynomolgus. I speak of these first, since the inoculations were made with the view of testing the question of the transmission of the pallida before—some time before—the announcement by Schaudinn that Metschnikoff had demonstrated the spirochætæ in a non-ulcerated lesion in this species, which was already developed at the time of the announcement of the discovery of the pallida. Thus far only one of my series has been fully studied for the pallida, which were found present in small numbers. Kraus,[36] of Vienna, has since followed the pallida through two monkeys, the second animal having been successfully inoculated with the virus of the first.

I have already carried you so far that I hesitate even to allude to another topic; and yet I cannot close this address without stating that although many negative control examinations have been made upon healthy persons and with divers pathological products, one or two writers[37] have claimed to find the pallida type of spiral in ulcerated tumors and in a non-syphilitic papilloma.[37a] The question of similarity of species found in these growths with the pallida is a dis-

36 Sonderabdruck a. d. akadem. Anzeiger, k. k. Akad. d. Wissenschaften in Wien, No. XVII. Ref. in Wiener klin. Wochenshrift, 1905, XVIII, 829; also with Prantschoff, idem., p. 942. Metschnikoff, Bull. de l'Institut Pasteur, 1905, III, 540.

37 Thesing, Berliner klin. Wochenschrift, 1905. XLII, 732; Münchener med. Woch., 1905, LII, 1337. Kiolemenoglou and V. Cube, idem., p. 1275. Hoffmann, Berliner klin. Woch., 1905, XLII, 880 and 1022. Bonhoff, idem., p. 1142. Borrell, Comp. rend. Soc. de Biologie, 1905, LVIII, 770. Moritz, Deutscher Archiv für klin. Medizin, 1905, LXXXIV, 459.

37a Of especial interest are the reports of Castellani (British Medical Journal, 1905, p. 1330) on parangi (yaws) in the lesions of which a spiral organism, bearing close superficial relationship to the pallida, has been found by him.

puted one, upon which I shall not enter. The means at our command at present, upon which to base a classification, are too few and inadequate to settle so important a discussion. It may, however, be remarked that there will doubtless be described among the host of spiral micro-organisms that must exist in nature, forms which approach more or less closely to the pallida type. But until cultivations can be secured and experimental inoculations tested we shall have to content ourselves with such considerations as those of morphology, staining reactions and relation to specific lesions, upon which data we must base our faith or disbelief that a great and epoch-making discovery has been made.

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